

Application No: 10/781,047  
Amendment dated November 17, 2008  
Amendment in Response to Final Office Action

6

57559(70207)

### REMARKS

Claims 6-22 and 25 are currently pending in this application. Claim 6 has been amended in this Amendment. No new matter has been added. Applicant and Applicant's attorney wish to express their appreciation to Examiners Weber and Shen for the telephonic interview held on November 12, 2008.

1. Claims 6-22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desiderio (J Chromatography B 1999;731:3-21) in view of Gerber et al. (Anal. Chem. 2001, 73:1651-1657).

The Examiner states, "Desiderio teaches a method for determining the presence/quantity of a target polypeptide in a mixture of different polypeptides by providing a mixture of human tissue extracts (from human with metabolic defects and normal control-page 5, 2.1 and 2.2), adding two known quantity of labeled (labeled differently with stable isotopes) peptide internal standard (page 5, 2.4), treating the mixture with a protease (trypsin-page 7, 2.6), fragmenting the peptides in the mixture by multistage mass spectrometry (tandem mass spectrometer-page 7, 2.8), determining the ratio of labeled fragments to unlabeled fragments and calculating the quantity of the target polypeptide in the mixture (page 7, 2.10.1 and page 8, 2.10.2). Peptides are separated by HPLC chromatograph (page 6, under Chromatograph, 2.5.1-2.5.4) and the fractions (eluent and co-eluent) are shown in Fig. 5-7. The presence/quantity of target polypeptide is diagnostic of a cell state where the cell state is representative of an abnormal physiological response (human pituitary macroadenomas-page 9, 3.1), and the target polypeptide is determined in at least two mixtures (abstract and for details see pages 9-14, pages 14-17).

Desiderio does not teach a single peptide internal standard in the method.

Gerber teaches a chromatography/mass spectrometry method for determining multiple enzyme activities in human cell lysates using a single internal standard (page 1652, right column, 2nd full paragraph). Gerber also teaches that the internal standard is chemically identical to the enzyme product and contain isotope (page 1652, right column, 2nd full paragraph, lines 4-7).

BOS2 705322.1

Application No: 10/781,047  
Amendment dated November 17, 2008  
Amendment in Response to Final Office Action

7

57559(70207)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Desiderio by using a single peptide internal standard in the method because protease activity is used and Gerber teaches the use of a single internal standard which is identical to the enzyme product (peptide as the product of protease) in the same chromatography/mass spectrometry method. One would have been motivated to make the modification because Desiderio et al. specifically described a method for determining the presence/quantity of a target polypeptide in a mixture of different polypeptides with two peptide internal standard, and would reasonably have expected success because Gerber teach the use of an internal standard that is chemically identical to the enzyme product in the same method (page 1652, right column, 2nd full paragraph). One internal standard is recognized as equivalent of two internal standard for the same purpose (see MPEP §2144.06), thus using one internal standard that is chemically identical to the enzyme product as taught by Gerber for the predictable result of determining the presence/quantity of a target peptide is obvious.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.”.

Applicants respectfully disagrees. It is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

BOS2 705322.1

Application No: 10/781,047  
Amendment dated November 17, 2008  
Amendment in Response to Final Office Action

8

57559(70207)

The Applicants have amended claim 6 (from which all other pending claims ultimately depend) to delete any reference to unmodified target polypeptides. Therefore, the claimed invention is directed to a method for determining the presence and/or quantity of **modified** (phosphorylated, acetylated, etc.) target polypeptides. There is no suggestion or motivation in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the cited reference to make the claimed invention (method for determining the presence and/or quantity of **modified** (phosphorylated, acetylated, etc.) target polypeptides), nor is there a reasonable expectation of success.

The Applicants' invention make use of the knowledge of how peptides behave in a mass spectrometer to select a peptide or peptides to monitor after proteolysis (a step required by the claims, but not mentioned or cited in the Desiderio or Gerber references). In addition, the Applicants go one step further to monitor posttranslationally-modified proteins (such as by phosphorylation or acetylation). Using synthetic peptides containing stable isotopes identical to the modified forms of the peptide sequence from the protein of interest, Applicants can find out the occupancy state of that modification on the protein.

Therefore, the Desiderio and Gerber references cannot be cited as a basis for an obviousness rejection of claims 6-22 and 25 in the present application. Applicants respectfully request reconsideration.

In view thereof, reconsideration and withdrawal of the §103 rejections are requested.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. Applicant's representative would like to discuss this case with the Examiner to learn if any outstanding issues remain after consideration of this Amendment. If the Examiner believes that a telephone conversation with Applicants'

BOS2 705322.1

Application No: 10/781,047  
Amendment dated November 17, 2008  
Amendment in Response to Final Office Action

9

57559(70207)

attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.


### CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Dated: November 17, 2007

Respectfully submitted,

Customer No. 21874

By   
Gregory B. Butler, PhD, Esq.  
Registration No.: 34,558  
EDWARDS ANGELL PALMER & DODGE  
LLP  
P.O. Box 55874  
Boston, Massachusetts 02205  
617-517-5595  
Attorneys/Agents For Applicant

BOS2 705322.1